(b) is produced from a cell line obtained from a mouse deficient in a gene encoding [said] a mouse p35 subunit or [said] p40 subunit of IL-12.

REMARKS

Claims 1-36 were pending in this application. Claims 1 and 29 have been amended to clarify that Applicants have always considered part of the claimed invention. In particular, Claims 1 and 29 have been amended to clarify that the mouse from which the antibody is produced is deficient for a gene encoding a *mouse* IL-12 p35 or p40 subunit. A copy of the pending claims is attached hereto as Exhibit A.

In the Office Action, the captioned application was restricted to the following three groups:

Group I: claims 1-33 directed to a human IL-12 antibody;

Group II: claim 34, directed to a method for producing an antibody that reacts with the human IL-12 p75 heterodimer; and

Group III: claims 35 and 36, directed to a method for producing a monoclonal antibody that reacts with the human IL-12 p75 heterodimer.

During a telephone conversation with the Examiner, Applicants provisionally elected with traverse the invention of Group I, claims 1-33, species B (HB-12447).

The election of Group I containing claims 1-33, species B (HB-12447) is made only to comply with the requirement, however restriction is improper. The basis for the restriction requirement stated in the Office Action is that the inventions are distinct because the claims of Group II and III are directed to different methods, and the claims of Group I are distinct from that of Group II and III because "the products as claimed can be made by a materially different process such as affinity purification or other detection assays."

With respect to the Examiner's requirement under 35 U.S.C. § 121 to elect a single disclosed species, there is no basis for requiring the election of a single species which is a member of a genus covered by a proper generic claim. The purpose of the genus is to cover separate distinct species of an invention. The fact that these species may be separately patentable does not provide a basis for restriction. As stated in MPEP § 802(a), one or more species of an invention may be specifically claimed in different claims in one application provided that the application also includes an allowable claim generic to all the claimed species and the claims to species in excess of one are written in dependent form or otherwise include all limitations of the generic claim.

Claims 1, 14 and 29 of the present application are generic to the claimed species, and the species claims are dependent on these generic claims. Thus, the Examiner is respectfully requested to withdraw the restriction requirement.

The Examiner has objected to the specification by contending that no statement appears in the specification reciting the earlier application to which the instant application claims priority under 35 U.S.C. § 119(e). Applicants assert that this contention is in error and respectfully direct the Examiner's attention to page 3, paragraph 11, of the transmittal sheet submitted with the application as originally filed, wherein Applicants requested that the instant specification be amended by inserting before the first line, "This application claims priority under 35 U.S.C. § 119(e) of provisional application(s) Serial No. 60/072,333, filed January 23, 1998." Accordingly, Applicants request withdrawal of the objection to the specification.

Entry of the amendments and remarks contained herein is respectfully requested.

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1. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

Claims 6-13, 21-28 and 30-33, drawn to particular monoclonal antibodies (Claims 6-13 and 21-28) or hybridomas (Claims 30-33), are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not adequately described in the specification in such a way as to enable one of skill in the relevant art to make and/or use the claimed invention. In particular, the Office Action contends that deposit of hybridomas producing the particularly recited monoclonal antibodies is required to practice the invention, and states that such deposit would satisfy the enablement requirements of Section 112. (Office Action, p. 4)

While not acquiescing to the propriety of the instant rejection, Applicants respectfully submit that the above-listed hybridomas are, indeed, deposited under the terms of the Budapest Treaty in a manner that satisfies the requirements set forth in 37 C.F.R. §§ 1.801-1.809. In particular, Applicants assure that the hybridoma cell lines HIL-12F3-5F2, HIL-12F3-16F2, HIL-12F3-20E11, and HIL-12F3-16G2 were deposited with the American Type Culture Collection (ATCC) on December 11, 1997, under designation numbers HB-12446, HB-12447, HB-12448 and HB-12449, respectively.

These hybridoma cell lines produce antibodies 5F2, 16F2, 20E11 and 16G2, respectively. These deposits are in complete compliance with the Deposit requirements as set forth in C.F.R. §§ 1.801-1.809. In this regard, and in particular to satisfy the requirements of 37 C.F.R. § 1.808, the Examiner's attention is directed to the statement by Applicants attorney, attached as Exhibit B, regarding the deposits. The Examiner's attention is further directed to the deposit contract (attached as Exhibit C) made in connection with the ATCC deposit of the hybridoma cell lines. In addition, the specification has been amended such that it fully complies with the requirements of 37 C.F.R. § 1.809(d).

For the reasons set forth above, the rejection under 35 U.S.C. § 1.112, first paragraph, has been overcome. As such, Applicants respectfully request that the rejection be withdrawn.

2. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn.

Claims 1-13 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite in view of the use of the term "immunologically reacts with." This rejection should be withdrawn for the reasons presented herein.

A claim to a compound satisfies the definiteness requirement of 112, second paragraph when one skilled in the art can recognize that a particular compound would be encompassed by the claim. As stated by the CCPA,

> the definiteness of the language employed must be analyzed-not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. In re Moore and Janoski, 169 USPQ 236, 238 (CCPA 1971).

The Office Action does not provide any sustainable basis for rejecting the present claims under 35 USC § 112, second paragraph. Applicants submit that the words "immunologically" "reacts" and "with" have well understood dictionary meanings which are known to those skilled in the art. In addition, the term has acquired a standard meaning in the art. Further, representative assays for measuring immunological reactivity are provided in the instant specification. See, *e.g.*, p. 7, ll. 11-25, of the instant specification. The claims of the present application, therefore, clearly apprise those skilled in the art of the subject matter of Applicants invention. Furthermore, the Board of Patent Appeals and Interferences has held that the recitation of the term "reacting" in a claim is not indefinite. See Ex parte Biel, 137 USPQ 315, 317 (Bd. Pat. App. & Int. 1962). Applicants respectfully submit that Claims 1-13 are sufficiently definite to satisfy the requirements of 35 U.S.C. 112, second paragraph.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-13 under 35 U.S.C. 112, second paragraph.

3. **The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn.**

Claims 1-5 and 29 are rejected under 35 U.S.C. § 102(b) as anticipated by Presky et al. ("Presky") as evidenced by Gately et al. ("Gately"). This rejection should be withdrawn for the reasons set forth below.

The basis for this rejection is that Presky discloses a heterodimer-specific humanized[1/] monoclonal antibody ("20C2") that reacts with IL-12 and not with p40. The Examiner states that the hybridoma producing 20C2 does not encode a gene for either human p35 or p40, and goes on to contend that recitation of the method by which the antibodies are produced carries no patentable "weight." First, it is respectfully pointed out that the claims recite--and have always recited-- antibodies produced by mice deficient for a gene encoding *mouse* p35 or p40. As discussed above, the claims have been amended to further clarify this point. Further, contrary to the Examiner's contention, the fact that the recited antibodies are produced by mice deficient in either mouse IL-12 p35 or p40 subunits does, indeed, confer novel attributes to the claimed antibodies, as discussed below, and as such, does carry patentable weight.

Clearly, the antibodies of Applicants' claimed invention are different from the 20C2 antibody described in the Presky et al. reference and U.S. Patent No. 5,780,597. Nowhere does the Presky reference or U.S. Patent No. 5,780,597 disclose or suggest Applicants' claimed antibodies or hybridomas. For an invention to be anticipated under 35 USC § 102 every element of the claim being examined must be shown in a single reference. As stated by the CAFC in Diversitech Corp. v. Century Steps, Inc.:

1/ As discussed below, Presky does not, in fact, disclose a *humanized* antibody.

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> For a prior art reference to anticipate terms of 35 USC 102, **every** element of the claimed invention must be identically shown in a **single reference**. 7 USPQ2d 1315, 1317 (Fed. Cir. 1988) (emphasis added).

As seen from the above-quoted passage, a rejection for anticipation under 35 U.S.C. § 102 is improper unless every element of the claimed invention is shown in a single reference. Thus, to be anticipated by the Presky reference, every element of Applicants' claimed invention must be identically shown in the Presky reference.

The p75 heterodimer-specific antibodies of the present invention are clearly different from previously reported IL-12 p75 heterodimer-specific antibodies, such as the 20C2 antibody, *e.g.*, such antibodies cannot substantially block IL-12 bioactivity, and/or fail to cross-react with rhesus monkey IL-12 heterodimer. Applicants' claimed invention is directed, in part, to antibodies to the human IL-12 p75 heterodimer produced from mice ("knock-out mice") deficient in the endogenous gene encoding the p35 subunit or the p40 subunit of IL-12, and, thus, cannot produce endogenous IL-12 p75 heterodimer. When immunized with the human IL-12 p75 heterodimer, knock-out mice very efficiently recognize the human IL-12 heterodimer as foreign and readily produce antibodies thereto. The utilization of IL-12 knock-out mice, in fact, results in production of antibodies that effectively neutralize IL-12 bioactivity.

The Presky reference and U.S. Patent No. 5,780,597 ("the '597 patent") disclose the 20C2 antibody, which is a rat monoclonal anti-human IL-12 antibody. Although the 20C2 antibody is reported to be a p75 heterodimer-specific antibody, unlike the antibodies of the present invention, the 20C2 antibody was not produced utilizing a knock-out mammal. The 20C2 antibody was <u>not</u> produced from rats deficient in the gene encoding the p35 or p40 subunit of IL-12. Nowhere does Presky or Gately disclose or suggest utilization of a knock-out mammal to produce the 20C2 antibody or any other IL-12 heterodimer specific antibody. Further, as demonstrated in the instant specification, the 20C2 antibody, *per se*, differs from antibodies produced by p35 or p40 knock-

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out mammals, *i.e.*, from the antibodies claimed herein. In particular, unlike the claimed antibodies, the 20C2 antibody fails to substantially neutralize human IL-12 bioactivity. See, *e.g.*, p. 2, l. 24, to p. 3, l. 2; Example 12, pp. 27-28, especially p. 27, ll. 19-21, and Figure 3; and Example 14, pp. 29-30, especially p. 30, ll. 1-4, and Figure 5. In addition, unlike antibodies claimed herein (see, *e.g.*, Claim 4), the instant specification also demonstrates that the 20C2 antibody fails exhibit cross-reactivity with rhesus monkey IL-12 (see, *e.g.*, Example 12, pp. 27-28, especially p. 27, l. 23, to p. 28, l. 3, and Figure 4).

Finally, especially with respect to Claim 5, in addition to the above, it is respectfully pointed out, that while Presky reports a mouse monoclonal antibody, contrary to the Examiner's contention, Presky does not, in fact, report a *humanized* antibody. Specifically, nowhere does Presky disclose or suggest a "humanized" monoclonal antibody. As described at page 16 of the instant application, "humanized" antibodies are produced from mammalian anti-human antibodies by modifying the mammalian antibodies to include regions of human antibodies. In this manner, the mammalian antibodies are made substantially non-immunogenic in humans. Nowhere does Presky disclose humanized antibodies.

Claims 1-4 and 29 are rejected under 35 U.S.C. § 102(b) as anticipated by Cytokine Bulletin; Claims 14-17 are rejected under 35 U.S.C. § 102(b) as anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as obvious in light of, Cytokine Bulletin. As above, the basis for these rejections is that the Cytokine Bulletin (p. 2) discloses an IL-12 heterodimer-specific monoclonal antibody that does not react with the p40 IL-12 subunit. For the same reasons presented above, this rejection should be withdrawn.

In particular, nothing in the Cytokine Bulletin teaches or suggests that the mouse antibody reported to be IL-12 heterodimer-specific was produced by mice deficient in the endogenous gene encoding the IL-12 p35 or p40 subunit. As such, the attributes conferred onto the claimed antibodies are not exhibited by the Cytokine Bulletin antibody. In particular, nothing in the

Cytokine Bulletin teaches or suggests that the reported mouse antibody substantially neutralizes human IL-12 bioactivity, nor does the Cytokine Bulletin teach or suggest that the reported mouse antibody exhibits cross-reactivity with rhesus monkey IL-12 heterodimer, each of which constitute non-obvious differences relative to the claimed antibodies.

Further, it is noted that the cited mouse antibody is an immobilized part of an ELISA kit that is designed to quantitatively measure the level of IL-12, *per se*, present in a sample, rather than measure the level via bioactivity. The Cytokine Bulletin, itself, distinguishes between bioactivity assays and the quantitative assay based on the reported mouse IL-12 antibody (see p. 2 of Quantikine human IL-12 Immunoassay section of Cytokine Bulletin). Thus, nothing in the Cytokine Bulletin suggests that the immobilized antibody would exhibit appreciable neutralizing activity, nor does the Cytokine Bulletin provides any motivation to even test for such activity.

For the reasons set forth above, the rejections under35 U.S.C. § 102, or, where appropriate, in the alternative, 35 U.S.C. § 103(a) should be withdrawn.

4. <u>The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn.</u>

Claims 5, 18 and 20 were rejected under 35 USC 103(a) as obvious over Cytokine Bulletin antibodies taught on p. 1 (IL-12 table) in view of prior art disclosed in the specification at page 16 (*i.e.*, a general reference teaching methods for producing humanized antibodies). The basis for this rejection is that the Cytokine Bulletin teaches a mouse anti-human IL-12 antibody that does not react with the p40 subunit of IL-12 and the prior art teaches procedures for humanizing murine antibodies. As discussed above, Claims 14-17 are rejected, in the alternative, as obvious over Cytokine Bulletin. These rejections should be withdrawn for the reasons set forth herein.

At the outset, with respect to the rejection of Claims 5, 18 and 20, it is noted that, while IL-12 antibody table of Cytokine Bulletin p. 1 may report mouse antibodies that do not react with

the p40 IL-12 subunit, the claimed antibodies, including the claimed humanized antibodies, of the present invention do not merely fail to react with p40, but are IL-12 p75 *heterodimer-specific* antibodies. None of the antibodies listed in the IL-12 antibody table of the Cytokine Bulletin exhibit or suggest such specificity. The fact that general methods of producing humanized antibodies existed at the time the instant specification was first filed does nothing to remedy the deficiencies in the antibodies of the cited IL-12 antibody table.

With respect to the rejection of Claims 14-17, as noted above, the cited mouse antibody is an immobilized part of an ELISA kit that is designed to quantitatively measure the level of IL-12, *per se*, rather than via bioactivity. The Cytokine Bulletin, itself, distinguishes between bioactivity assays and the quantitative assay based on the reported mouse IL-12 antibody (see p. 2 of Quantikine human IL-12 Immunoassay section of Cytokine Bulletin). Thus, nothing in the Cytokine Bulletin suggests that the immobilized antibody would exhibit appreciable neutralizing activity, nor does the Cytokine Bulletin provides any motivation to even test for such activity.

With respect to each of the rejected claims, Applicants assert that methods conventionally used to make antibodies, such as antibodies to the human IL-12 p75 heterodimer, cannot be used to make the claimed antibodies. On the other hand, when techniques as taught in the instant specification are utilized, *i.e.*, when IL-12 antibodies are generated using a mammal deficient in the gene encoding endogenous p35 or p40 IL-12 subunit, it is possible to produce antibodies exhibiting the characteristics of the claimed antibodies, *e.g.*, IL-12 heterodimer-specific antibodies that substantially neutralize human IL-12 bioactivity. The cited prior art fails to teach or suggest such a "primed" starting material to produce antibodies to the human IL-12 heterodimer. Without such a teaching, which would place the invention in the possession of the public, it is clear that the invention is not obvious.

Section 103 requires that in making a determination of obviousness, one must consider the invention as a whole. Attention is directed to the decision of the Court in In re Hoeksema, 158

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USPQ 596 (CCPA 1968) where the claimed compound was rejected over a structurally related compound of the prior art. In holding that the claimed compound was patentable since the Patent Office had not made a showing that there was a known or obvious way to make this claimed compound, the CCPA stated:

> We are certain, however, that the invention as a whole is the claimed compound *and* a way to produce it . . . .There has been no showing by the Patent Office in this record that the claimed compound can exist because there is no showing of a known or obvious way to manufacture it; hence, it seems to us that the 'invention as a whole' which section 103 demands that we consider, is not obvious from the prior art of record. 158 USPQ at 600.

Likewise, nothing in the cited prior art teaches any method whereby one could obtain the claimed antibodies of this invention in that nothing in the cited prior art teaches or suggests a method by which to produce antibodies exhibiting the characteristics of the presently claimed antibodies. The Cytokine Bulletin does not provide any example or procedure whereby one could obtain the claimed antibodies to the human IL-12 p75 heterodimer.

For the prior art to constitute a rejection of the claimed antibodies, the prior art must place the claimed invention "in the possession of the public." Since the prior art fails to suggest, or certainly enable, the production of antibodies that exhibit the characteristics of the claimed antibodies (*e.g.*, IL-12 heterodimer specificity exhibiting substantial neutralization of human IL-12 bioactivity and/or cross-reactivity with rhesus monkey IL-12), it fails to place the claimed invention in the possession of the public. As stated by the CCPA in reversing a rejection in In re Hoeksema

> if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention is made, it may not be legally concluded that the compound itself is in the possession of the public. 158 USPQ 596, 601 (CCPA 1968).

Nothing has been set forth in the Office Action to show where the cited prior art provides a method for producing the antibodies of the claimed invention. Attention is directed to Ex Parte Stern 13 USPQ2d 1379 (BPAI 1989) in which the Patent Office Board of Appeals stated that

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evidence is required, rather than a mere assertion that it would be obvious to one skilled in the art to produce the claimed invention. In Ex Parte Stern, the difference between the claimed invention and the prior art was in the degree of purification. In the Stern case, the Examiner asserted that the claimed invention was "deemed" obvious due to advances in technology which made purification obvious. In holding that without any means disclosed in the prior art to obtain such purified compound, the rejection under Section 103 must fall, the Board of Appeals stated

> The examiner should be aware that "deeming" does not discharge him from the burden of proving the requisite factual basis and establishing the requisite motivation to support a conclusion of obviousness . . . . the examiner's reference to unidentified phantom prior art techniques falls far short of the mark. 13 USPQ2d at 1381.

No proof has been provided to support a conclusion of obviousness, therefore, the rejection improperly deems Applicants' claimed invention obvious. Reliance upon Applicants' disclosure and phantom prior art techniques cannot be used to provide the requisite evidence of obviousness. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the preceding remarks, Applicants submit that this application is in condition for allowance. Applicants respectfully request reconsideration and withdrawal of each ground of rejection set forth in the June 17, 1999 Office Action and earnestly solicit favorable action on all pending claims.

Respectfully submitted,

Dated: December 17, 1999

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